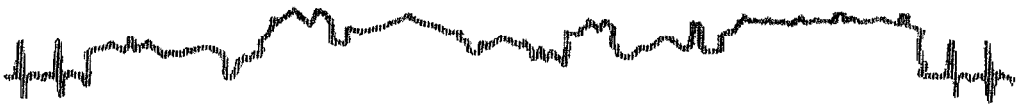

STOCKBRIDGE FAMILY MEDICINE

12/19/03

To the FDA,

I am petitioning the FDA to have all food products which contain gluten, a natural, but known *toxic* polypeptide, be marked with a simple but clear warning, e.g. *a logo of wheat or something similar,*

I have had clinical experience with gluten sensitive patients who can have protean clinical manifestations, which are often difficult to diagnose. (See enclosed articles from the NEJM regarding this health problem)

I believe that the presence of gluten in so many food products is a *major* health problem that remains below the radar of the medical establishment given that the prevalence of gluten sensitivity is about 1 in 300 people, combined with the long term toxicity of gluten in sensitive individuals.

I submit that food labeling of gluten containing foods be considered and implemented. There is no environmental impact of doing this, and the only information that I know to which this petition would be unfavorable is resistance from wheat farmers given that gluten is a toxic substance in susceptible individuals.

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition which are unfavorable to the petition.

Yours Truly,

Todd R. LePine, M.D.

Todd R. LePine, MD

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EDITORIALS

Celiac Disease — How to Handle a Clinical Chameleon

Alessio Fasano, M.D.

Celiac disease is an immune-mediated enteropathy triggered by the ingestion of gluten-containing grains (including wheat, rye, and barley) in genetically susceptible persons. The disease is associated with HLA-DQ2 in 90 to 95 percent of cases and with HLA-DQ8 in 5 to 10 percent of cases and is self-perpetuating in the continued presence of gluten.[1] It is the interplay between genes (both HLA and other types) and environment (i.e., gluten) that leads to the intestinal damage that is typical of the disease.[2] Under physiologic circumstances, this interplay is prevented by competent intercellular tight junctions, structures that limit the passage of macromolecules (including gluten peptides) across the intestinal epithelial barrier. Recent evidence suggests that the gluten-induced up-regulation of zonulin, an intestinal peptide involved in the regulation of tight junctions, is responsible, at least in part, for the aberrant increase in gut permeability that is characteristic of the early phase of celiac disease[3] and the subsequent abnormal passage of gluten into the lamina propria. The protein is deamidated by tissue transglutaminase in the lamina propria and is then recognized by antigen-presenting cells bearing HLA-DQ2 or DQ8, thereby triggering the autoimmune reaction of celiac disease.[2] Given the undisputable role of gluten in causing inflammation and immune-mediated tissue damage, celiac disease represents a unique model of autoimmunity in which, in contrast to all other autoimmune diseases, a close genetic association with HLA-DQ2, DQ8, or both; a highly specific humoral autoimmune response (autoantibodies against tissue transglutaminase); and most important, the triggering environmental factor (gluten) have all been identified. This information provides the rationale for the treatment of the disease based on complete avoidance of gluten-containing grains, a task complicated by the lack of a clear food-labeling policy.

Epidemiologic studies conducted during the past decade, using specific and sensitive serologic tests, have revealed that celiac disease is one of the most common lifelong disorders in both Europe[4] and the United States.[5] The clinical presentation of this condition can range from the typical syndrome of malabsorption (chronic diarrhea, weight loss, and abdominal distention) to symptoms and conditions that can affect any organ system (Table 1).[5] Since the onset of celiac disease may be atypical or even silent, many cases remain undiagnosed and thus carry a risk of long-term complications, including osteoporosis, infertility, and cancer.

In this issue of the Journal, the article by Mäki and coworkers confirms that celiac disease often goes undiagnosed, even in a country such as Finland, where the level of awareness of the disease is high.[6] Using the most sensitive and specific serologic tests available — tests for endomysial and tissue transglutaminase antibodies — combined with HLA typing, the authors screened a cohort of children whose serum samples had been collected seven years earlier. Fifty-six had positive serologic tests, only 10 (18 percent) of whom had been given a diagnosis of celiac disease between the serum

Table 1. Atypical Clinical Manifestations of Celiac Disease.

Diabetes
Anemia
Osteoporosis or other bone diseases
Chronic fatigue
Autoimmune disorders
Gastrointestinal cancer
Dermatitis herpetiformis
Behavioral changes
Irritable bowel
Miscarriage
Neurologic symptoms (including ataxia)

collection in 1994 and screening in 2001. In 27 children, the diagnosis was confirmed by an intestinal biopsy at follow-up in 2001, suggesting that the prevalence of celiac disease among Finnish children is 1 case in 99 children. The prevalence of the celiac disease trait, defined as seropositivity for autoantibodies and an HLA haplotype associated with celiac disease, was even higher: 1 case in 67 children.

These results raise many interesting questions. How can a disease that, if not treated, is associated with a high rate of morbidity and increased mortality not be segregated by genetic evolution and thus remain one of the most frequent genetically based disorders in humans?[2] One possible explanation is that gluten, a protein introduced in large quantities into the human diet only after the advent of agriculture, activates "by mistake of evolution" mechanisms of innate immunity (such as the zonulin pathway[7,8]) that are too important to the survival of the species to be eliminated.

Another question concerns the variables that dictate the duration of clinical latency and the type of symptoms that occur once celiac disease becomes clinically apparent. In recent years, the age at the onset of symptoms has increased and the clinical presentation has changed. These changes seem to be associated with the introduction of smaller amounts of gluten into the diet at older ages.

A third question concerns the complications of untreated celiac disease. Multiple studies that have focused on the biochemistry and toxicity of gluten-containing grains and the immune response to these grains suggest that patients with celiac disease should be treated, whether or not they have symptoms or associated conditions. However, no well-designed prospective clinical studies have addressed this point, nor do such studies seem likely to, given the ethical implications. Nevertheless, there is general agreement that persistent mucosal injury, with or without typical symptoms, can lead to serious complications in adults with celiac disease who do not strictly comply with a gluten-free diet.[2]

Perhaps the most controversial issue raised by the findings of Mäki and coworkers is the question of who should be screened for celiac disease. The prevalence of the disease and the burden of illness related to this condition, particularly if it is not treated, are so high as to potentially support a policy of screening of the general population. Celiac disease satisfies the five criteria of the World Health Organization for justifying general screening.[9] First, early clinical detection of the disease could be difficult, as suggested by Mäki et al. Second, with an overall prevalence approaching 1 percent,[7] celiac disease is a common disorder, causing substantial morbidity in the general population. Third, the screening tests for celiac disease are highly sensitive and specific, as demonstrated by many reports in the literature, including that by Mäki et al. Fourth, a treatment for the disease — a gluten-free diet — is available. Finally, if it remains unrecognized, celiac disease could increase the risk of life-threatening complications that are difficult to manage, such as intestinal lymphoma.

Nevertheless, the justification for screening of the general population for celiac disease will depend on the results of comprehensive, well-performed cost-effectiveness analyses. Although it is well established that complications may develop in the absence of treatment, the natural history of undiagnosed celiac disease remains unclear. Published studies have necessarily been limited to patients who have received a clinical diagnosis, an approach that ultimately leads to a biased estimate of the risks.[2] Despite the high sensitivity of the serologic tests for celiac disease, the positive predictive value of these tests decreases when they are used in the general population rather than in groups at increased risk.[2]

The appropriate age for screening and the need for periodic repetition of screening to rule out late-onset gluten sensitization are unclear.[2] The difficulties of treating patients with apparently silent celiac disease should also be considered. A five-year follow-up study revealed a 30 percent decrease in adherence to the gluten-free diet among patients in whom the disease was detected by screening, as compared with age-matched patients with symptomatic celiac disease identified during a regular diagnostic workup.[10] At the moment, the best epidemiologic approach to the diagnosis of celiac disease seems to be a systematic process of case-finding in which patients with symptoms or conditions, both typical and atypical (Table 1), known to be associated with the disease are targeted. Because of the high rate of morbidity related to untreated celiac disease and the typical delay in diagnosis,[7] increased awareness of the disease on the part of health care professionals, especially primary care physicians, and a low threshold for the use of serologic tests are pivotal both to alleviate the social and personal costs of the disease and to increase the quality of life of the many patients affected by celiac disease.

Dr. Fasano reports having served as a paid lecturer to Prometheus.

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Celiac Disease — The Villain Unmasked?

Ross McManus, Ph.D., and Dermot Kelleher, M.D.

Celiac disease (also known as celiac sprue and gluten-sensitive enteropathy) is a common autoimmune condition triggered by ingesting one of several related proteins found in wheat, barley, and rye: the gliadins, hordeins, and secalins. In susceptible persons, ingestion of these proteins leads to infiltration of the intestinal mucosa by both intraepithelial CD8+ lymphocytes and CD4+ lamina propria lymphocytes and, ultimately, to crypt hyperplasia and villous atrophy.[1,2] Symptoms vary — malabsorption of food by the intestine, diarrhea, and failure to thrive are typical in affected children, and symptoms in adults can include depression and anemia. A gluten-free diet alleviates these symptoms, although adherence to such a diet can be difficult. Shan and colleagues[3] have recently identified a peptide that probably initiates the disease, raising the possibility that strategic inroads can be made into the disorder.

There is increasing evidence that CD4+ T cells mediate the pathogenic process in celiac disease. First, the principal determinants of genetic susceptibility are the highly variable HLA class II DQA and DQB genes located in the major histocompatibility complex. These genes (specifically the combination of variant alleles HLA-DQA1*0501 and DQB1*0201) encode the HLA-DQ2 class II protein molecule, which presents peptides to and binds CD4. A less prevalent determinant of susceptibility is the HLA-DQ8 variant. Second, HLA-DQ2–restricted T-cell clones that are specific for gliadin have been isolated from the small intestines of patients with celiac disease. However, these clones produce only small amounts of cytokines, and the mechanism by which gliadin peptides bind with high affinity to the HLA-DQ2–binding groove has only recently become clear.

The presence of endomysial autoantibody is another indicator of celiac disease, and the identification of tissue transglutaminase as the target of this antibody[4] has been enlightening. This enzyme is expressed on the subepithelial layer of intestinal epithelium, where it deamidates the glutamine residues in gliadin, resulting in glutamic acids. Deamidated peptides adhere strongly to the binding grooves of HLA-DQ2 and DQ8 molecules and elicit strong T-cell responses.[5]

Although the ingested proteins responsible for celiac disease may carry epitopes capable of activating T cells, they are also substrates for proteolytic degradation by gastrointestinal enzymes and thus should be fully digested before any exposure to the immune system could possibly occur. Therefore, the question of whether peptides constituting T-cell epitopes can survive the degradations of a low pH and proteolytic enzymes has critical implications for their functional relevance. Shan et al.[3] showed that one 33-amino-acid (33-mer) peptide survives transit through the digestive enzymatic milieu and arrives intact in the small intestine. In a series of elegant experiments, they demonstrated that this 33-mer resists digestion by gastric and intestinal proteolytic enzymes for extended periods in vitro. The peptide is resistant — both in vitro and in vivo — to digestion by brush-border enzymes of the small intestinal mucosa of rats and humans, although these enzymes normally reduce any remaining peptides to single amino acids or small peptides of about two or three residues before they are absorbed.

The 33-mer carries multiple copies of three epitopes that are immunogenic in patients with celiac disease (Fig. 1). Furthermore, the 33-mer has a very high affinity for tissue transglutaminase. Shan et al. found that once it was deamidated by tissue transglutaminase, the 33-mer elicited a response from each of 14 polyclonal T-cell lines derived from different patients with celiac disease. It therefore has many, if not all, of the properties required to initiate a response in patients with celiac disease. If

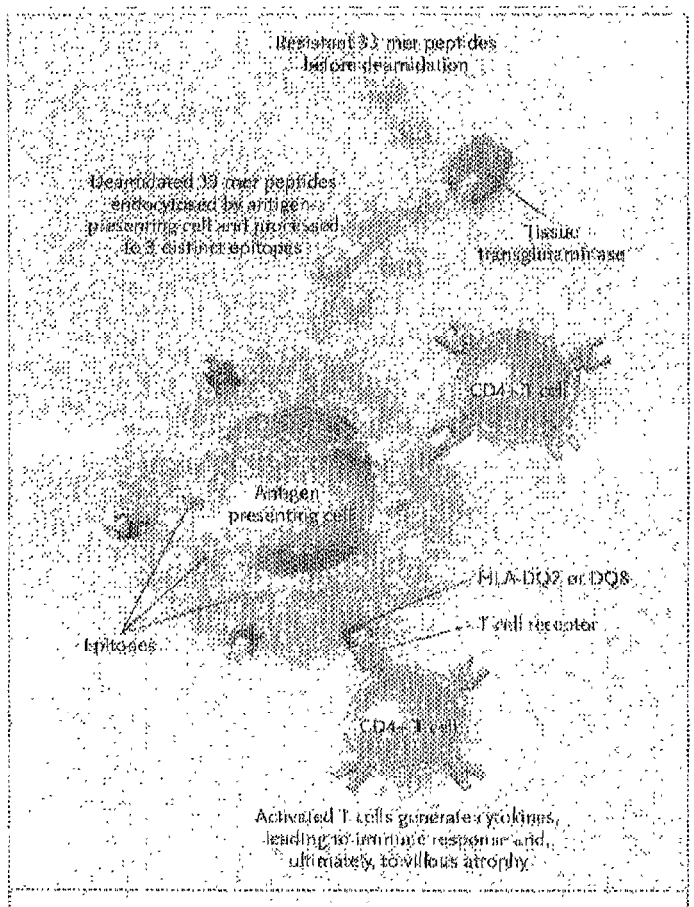

Figure 1. Activation of the Immune Response by a 33-mer Peptide Present in Gliadin.

The 33 amino-acid (33-mer) peptide arrives intact in the small intestine, where it undergoes deamidation by tissue transglutaminase. By means of endocytosis, the deamidated peptide then enters the antigen-presenting cell, where it is processed to three epitopes that bind to the HLA-DQ2 or DQ8 molecule and are subsequently recognized by T-cell receptors of CD4+ T cells. The activated CD4+ T cells generate cytokines, prompting the immune response and, ultimately, the villous atrophy and crypt hyperplasia that are characteristic of celiac disease.

survives the digestive tract, is a good substrate for tissue transglutaminase, is loaded onto HLA-DQ molecules, and activates T cells — which may then drive the characteristic immune response in the small intestinal mucosa. Similar peptide sequences are present in the hordeins and secalins.

Of potential therapeutic consequence is the finding that the 33-mer is broken down by a bacterial prolyl endopeptidase, raising the encouraging possibility of alternatives to a gluten-free diet (perhaps including genetic modification of the offending sequence) for the treatment of celiac disease. Successful clinical trials of such peptidases would provide final proof of the hypothesis that the 33-mer is central to the molecular pathologic process of celiac disease.

Despite these welcome findings, many questions remain. For example, up to 30 percent of persons of North European ancestry express HLA-DQ2, but celiac disease develops in only a small proportion of these carriers. There is some evidence, however, that the disease may be underdiagnosed, as reported by Mäki et al.[6] in this issue of the *Journal*. Although there is a pronounced familial aggregation of celiac disease, the pattern of inheritance is complex. Hence, it is clear that other genetic and possibly environmental influences have yet to be identified. The role of intraepithelial CD8+ lymphocytes (which do not bind class II molecules of the major histocompatibility complex) in the pathogenesis of the disease also remains to be determined. These questions notwithstanding, the identification of a pathogenetic pathway involving autoantibodies and cell-based immunity in celiac disease demonstrates the importance of research on principles of immunology and offers new hope for the understanding of other complex disorders.

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